

## Obesity-related blood brain barrier changes in obese Zucker rats

Daniele Tomassoni<sup>1</sup>, Seyed Khosrow Tayebati<sup>2</sup>, Monica Ciriaci<sup>2</sup>, Federica Cognigni<sup>1</sup>, Francesco Amenta<sup>2</sup>

<sup>1</sup> School of Biosciences and Veterinary Medicine, University of Camerino, Camerino, Italy - <sup>2</sup> School of Medicinal and Health Products Sciences, University of Camerino, Camerino, Italy

The blood brain barrier (BBB) is the site of exchange between blood and the nervous tissue. Damage of it may impair physiological balance between blood stream and nervous tissue.

Metabolic syndrome (MetS) is defined by several interconnected physiological, biochemical, and metabolic factors directly related to obesity. It increases the risk of atherosclerotic cardiovascular and cerebrovascular disease and of all cause mortality.

Obese Zucker rats (OZR), with a mutation in leptin receptor, represent a model of obesity exhibiting diabetes and moderate arterial hypertension. In OZR hyperglycaemia, hyperinsulinaemia and hyperlipidaemia occur simultaneously.

This work had characterized BBB and endothelial alterations of OZR compared to their non-obese cohort lean Zucker rats (LZR) for assessing the occurrence of an eventual cerebrovascular injury. Brains of male OZR and LZR of 12, 16 and 20 weeks were processed for the immunochemical and immunohistochemical detection of different BBB markers.

The water channel protein Aquaporin-4 (AQP4) and the glucose transporter protein-1 (GLUT1) involved in the glucose passage across the BBB endothelial cells were investigated. The expression of adhesion molecules intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and platelet-endothelial cell adhesion molecule-1 (PECAM-1) was also assessed within cerebrovascular endothelium as a marker of inflammation.

In intracerebral arteries of older OZR, a decrease of lumen area with an increase of wall area was found. BBB of older OZR revealed an augmented expression of AQP4 probably related to an edema formation. A downregulation of GLUT1 was observed in OZR of 12 weeks of age. This may represent the adaptive reaction to prevent excessive glucose entering in neurons. On the contrary, in older OZR an obvious increase in the expression of GLUT1 was found. These phenomena are probably related to vascular inflammation as confirmed by the increase of ICAM-1 and VCAM-1 expression in the endothelium of older OZR.

The above evidence shows that OZR develop specific BBB changes. This could contribute to clarify the pathophysiology of nervous system damage reported in obese individuals. OZR may represent an useful animal model for assessing the influence of obesity/MetS on the brain and the possible correlation of it with neurodegenerative disorders.

---

### Keywords

Obesity; Obese Zucker rat; Cerebrovascular tree; Morphology.